REMARKS

Applicant respectfully requests entry of the amendments and remarks submitted herein. Claims 59-62 have been added. Therefore, claims 24-30 and 39-63 are pending.

Rejection under 35 U.S.C. § 112, Second Paragraph

The Examiner rejected Claims 24-30 and 39-58 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

This rejection is respectively traversed. At page 2-3 of the Office action the Examiner stated that the independent claims recite two functional limitations (1 and 2) which contradict each other in terms of half-life (i.e. 1) a lower half-life that is at least as great as the free drug and 2) and an upper half-life that is less than 14 hours in a rat). Applicant notes that this claimed range of half-lives is in fact a single embodiment of the invention as described in the Summary of the Invention (page 3). The application clearly states that these half-lives are to be used together (emphasis added) to define a range which is an embodiment of the invention. Applicant reiterates that these half-lives are not contradictory or mutually exclusive but serve to provide a functional range clearly defining the metes and bounds of the invention as claimed. Furthermore, Applicant asserts that the elimination half-life range recited in the claims is proper as provided for in M.P.E.P 2173.05(g) and not indefinite. The claims clearly recite a formulation wherein the half-life of the therapeutic agent as part of the formulation is at least as long as long as the therapeutic agent in the absence of the liposome but less than about 14 h in the rat as part of liposome formulation. Accordingly, Applicant requests the withdrawal of the rejection of claims 24-30 and 39-58. Applicant notes that new claims 59-62 are analogous to claims 24-28 and recite only the upper half-life limit (i.e. wherein the elimination half-life of the therapeutic agent when administered as part of the formulation is less than about 14 hours in a rat). These claims are patentable for reasons similar to those discussed above; Applicant respectfully requests the Examiner to exam these claims independently.

At page 3, second paragraph of the Office action the Examiner stated that it is unclear whether the ratios recited in the instant independent claims are based on weight ratios or mole

ratios. Applicant notes that the tables of Examples 1-3 at pages 21-23 of the application all specify the ratios of lipids as mole ratios. Applicant notes that the ratios recited in the instant claims and shown at page 11 are not designated as weight ratios as suggested by the Examiner.

Rejection under 35 U.S.C. § 103(a)

The Examiner rejected Claims 24-30 and 39-58 under 35 U.S.C. 103(a) as being unpatentable over Lopez-Berestein by itself or in combination with Allen, Fujii, and O'Rear individually or in combination.

This rejection is respectfully traversed. As discussed in the response to the previous Office action the Lopez-Berestein liposomes differ significantly from the liposomes recited in the instant claims (summarized below). Furthermore, the newly applied references, Allen, Fujii and O'Rear do not remedy the deficiencies of Lopez-Berestein.

Claim 24 recites a liposome that comprises HSPC:cholesterol:DSPG in a ratio of about 4:1:0.1. Thus the ratio of HSPC:DSPG is 4:0.1 (i.e. 40:1). In contrast, Lopez-Berestein recites at column 8, lines 4-7, liposomes comprising dimyristoyl phosphatdylglcerol and dimyristol phosphatidylcholine in ratios of about 1:10 and 10:1 and more preferably in a ratio of about 3:7. Thus, the specific lipids are different and the ratio of phosphatidylglycerol lipids to phosphatidylcholine lipids is significantly different even when comparing the most similar ratios (40:1 versus 10:1). The Examiner has not provided any scientific reasoning why one would be led to a ratio of 40:1 from the Lopez-Berestein ratio of 10:1. Accordingly, claim 24 would not be obvious when the art teaches a ratio of about 10:1.

As characterized by the Examiner the newly applied references Allen, Fujii and O'Rear discuss liposomes that include cholesterol. However, these citations do not speak to the difference between the ratios of phosphatidylglycerol lipids to phosphatidylcholine lipids as discussed above and thus do not remedy the deficiencies of Lopez-Bernstein. These references all utilize different liposomal constituents and result in significantly different liposomes. The liposomes of Allen, which use egg lecithin are significantly less stable than the liposomes described in the instant invention. These liposomes leak due to osmotic stress while the liposomes described in the instant claims do not. The liposomes of O'Rear rely on the permeability of the liposome to release the active agent and thus permeability of the

biocompatible layer is a key feature. In contrast, the liposomes recited in the instant claims release the therapeutic agent via clearance of the liposome. Lastly, the liposomes of Fujii are highly stable and thus are slow release liposomes. The liposomes of the instant invention are intermediate release liposomes. Accordingly, the liposomes of Allen, Fujii and O'Rear when combined with the liposomes of Lopez-Berestein do not teach or suggest the liposomes recited in the instant claims.

Claims 24-30 and 39-58 recite a functional element comprising an elimination half-life range with an lower and upper limit (i.e. at least as long as the elimination half-life of the therapeutic agent when administered to the same animal in the absence of the liposome and less than about 14 hours in the rat). Claims 24-30 and 39-58 also recite a lipophobic therapeutic agent. In contrast, Lopez-Berestein, teach a liposome agent comprising hamycin. Hamysin is hydrophobic (i.e. lipophilic) and is embedded in the bilayer of the liposome and not present in the interior of the liposome. Thus Lopez-Berestein, when considered alone, or in combination with Allen, Fujii and O'Rear fail to teach or suggest either the terminal half-life range or the lipophobic therapeutic agent of claims 24-30 and 39-58.

Claims 29-30 recite specific therapeutic agents (i.e. cisplatin, amikacin and vancomycin). Lopez-Berestein by itself or in combination with Allen, Fujii, and O'Rear do not teach or suggest the therapeutic agents of these claims.

Accordingly, the withdrawal of the rejection of claims 24-30 and 39-58 is respectfully requested. Applicant also notes new claims 59-63 are independently patentable for reasons similar to those discussed above.

The Examiner rejected Claims 24-30 and 39-58 under 35 U.S.C. 103(a) as being unpatentable over Hersch by itself or in combination with Allen, Fujii, or O'Rear individually or in combination.

This rejection is respectfully traversed. Hersch at column 6 lines 11-17 recites liposomes with a preferred ratio of HSPC:cholesterol:DSPG of about 2:1:0.1 and the drug to total lipid ratio is about 1:4. Applicant submits that the Office action has provided no text reference or knowledge why the above ratio suggests an HSPC:cholesterol:DSPG ratio of 4:1:0.1 as recited in claim 24. According claim 24 is not obvious over Hersch. Furthermore, claims 24-30 and 39-58 recite an elimination half-life range with a lower and

upper limit as discussed above. This elimination half-life range further defines the metes and bounds of claims 24-30 and 39-58. Hersch does not teach or suggest this functional element of the claims. In contrast, the compositions discussed by Hersch provide long-circulating liposomes. Specifically, Hersch reports at Example 5 (Table 5) that liposomes prepared therein provide a significant plasma concentration of amikacin at 14 and 24 h after administration. Thus, Hersch, when considered alone teaches away from claims 24-30 and 39-58. The newly applied references Allen, Fujii and O'Rear, characterized above, do not remedy the deficiencies of Hersch.

Accordingly, withdrawal of the rejection of claims 24-30 and 39-58 is respectfully requested. Claims 29 and 30, which recite specific therapeutic agents, are not obvious over the applied references for the same reasons as discussed above. Applicant also notes that new claims 59-63, which also recite a functional element (i.e. upper half-life limit) are independently patentable.

The Examiner rejected Claims 24-30 and 39-58 under 35 U.S.C. 103(a) as being unpatentable over Lopez-Berestein in view of Allen, Fujii or O'Rear individually or in combination as set forth above, in combination with Hersch cited above.

This rejection is respectfully traversed. As discussed above Lopez-Berestein describe liposome systems that are very different than the liposomes recited in the instant claims. Lopez-Berestein describes a system wherein a hydrophobic therapeutic agent is trapped in the lipid bilayer of the liposome. In contrast, the instant claims recite a lipophobic (i.e. a hydrophilic) therapeutic agent. In addition, claim 24 of the instant application recites a formulation comprising a ratio of HSPC:cholesterol:DSPG in a ratio of 4:1:0.1 (i.e. the ratio of HSPC:DSPG is 4:0.1 or 40:1) and claim 28 recites a formulation comprising a ratio of DMPC:cholesterol:DSPG in a ratio of 2:1:0.1 (i.e. the ratio of DMPC:DSPG is 2:0.1 or 20:1) In contrast, Lopez-Berestein (column 8, lines 4-7) recites a ratio of dimyristoyl phosphatidyl glycerol to dimyristoyl phophatidyl choline of 1:10 and 10:1 and preferably in a ratio of 3:7. Applicant submits that the Office action has supplied no text, reference or knowledge why one skilled in the art would find the lipids and ratio of lipids of claim 24 obvious over the different lipids and different ratios of Lopez-Berestein. Similarly, Applicant submits that the

Office action has supplied no text, reference or knowledge why one skilled in the art would find the ratio of lipids of claim 28 obvious over the different ratios of Lopez-Berestein. Allen, Fujii and O'Rear, characterized above, do not remedy these deficiencies of Lopez-Berestein. Also, for reasons discussed above, the composition recited at column 6, lines 11-17 of Hersch does not remedy the deficiencies of Lopez-Berestein.

Claims 24-30 and 39-58 all recite an elimination half-life range as a functional element. Applicant notes that none of the applied references teach or suggest this functional element. Accordingly, the Office action has failed to make a prima facie case of obviousness over the rejected claims. Applicant respectfully requests the withdrawal of the rejection of claims 24-20 and 39-58.

The Examiner rejected Claims 29 and 44-48 under 35 U.S.C. 103(a) as being unpatentable over Lopez-Berestein, Allen, Fujii and O'Rear individually or in combination; or Hersch, Allen, Fujii, O'Rear individually or in combination also as set forth above, further in view of Abra.

This rejection is respectfully traversed. Claim 29, is dependent on claims 24-28. The Office action has failed to state a prima facie case of obviousness for claim 29 for reasons analogous to those stated above. In addition, claim 29 is independently patentable as none of the cited references (i.e. Lopez-Berestein, Allen, Fujii, O'Rear, or Hersh) teach or suggest "cisplatin". Abra states at column 1, lines 63-67 "cisplatin, however is difficult to efficiently entrap in liposomes because of the drug's low aqueous solubility, approximately 1.0 mg/mL at room temperature and low lipophilicity, both of which contribute to a low drug/lipid ratio." Thus Abra teaches away from claim 29. Accordingly, withdrawal of the rejection of claim 29 and claims 44-48 is respectfully requested.

The Examiner has also rejected Claims 25-26, 28, 40, 41, 43, 55-56 and 58 under 35 U.S.C. 103(a) as being unpatentable over Hays by itself or in combination with Hersch, Allen, Fujii or O'Rear individually or in combination.

This rejection is respectfully traversed. Hays describe liposome systems that are very different than the liposomes recited in the instant claims. The liposomes described by Hays would not provide liposomes with intermediate release properties. Although Hays describes a

liposome comprising DEPC and mentions in a broad manner that cholesterol may be present, no guidance is provided relative to the amounts of cholesterol that would lead to a liposome with intermediate release of a lipophobic agent in regard to claim 25. Likewise, although Hays mentions negatively charged phospolipids, Hays does not suggest or teach either the lipids recited in instant claims 26 and 28 or the ratios of the lipids to one another. The proper selection of both of these elements provides for liposomes that have intermediate release properties consistent with the functional element of the claims. The cited references Allen, Fujii or O'Rear discuss the inclusion of cholesterol within liposomes but do not teach or suggest the preparation of intermediate release liposomes such as those described in the rejected claims. Furthermore, Hersch does not teach or suggest the compositions or ratios of the formulations of claims 26 or 28. Therefore, there is no explicit or inherent reason to combine the cited references to arrive at the liposomes of the rejected claims. Furthermore, there is no discussion or preparation of any intermediate release liposomes in any of the cited documents as described at page 3-4 of the application prior to Applicants discovery.

As discussed above claims 25-26, 28, 40, 41, 43, 55-56 and 58 all recite an elimination half-life range as a functional element. Applicant notes that none of the applied references teach or suggest this functional element. Accordingly, the Office action has failed to make a prima facie case of obviousness over the rejected claims. Therefore, withdrawal of the rejection of claims 25-26, 28, 40, 41, 43, 55-56 and 58 is appropriate and requested.

The Examiner rejected Claims 27, 42, 47, 52 and 57 under 35 U.S.C. 103(a) as being unpatentable over Hays alone or in combination with Hersch, Fujii, or O'Rear individually or in combination as set forth above, further in view of Anaissie.

This rejection is respectfully traversed. Claims 27, 42, 47, 52 and 57are not obvious over Hays alone or in combination with Hersch, Fujii, or O'Rear for reasons similar to those discussed above. Anaissie does not teach or discuss liposomes with intermediate release properties or liposomes with an elimination half-life range as described in the rejected claims and therefore does not remedy the deficiencies of Hays alone or in combination with Hersch, Fujii, or O'Rear. Accordingly, withdrawal of the rejection of claims 27, 42, 47, 52 and 57 is respectfully requested.

Summary Statement

Applicant acknowledges that there is broad disclosure pertaining to the science of liposomes and liposomes comprising therapeutic agents. However, it is crucial to note that the number of variables within this area of science (i.e. therapeutic liposomes) is truly large. Not only can liposomes can be made from a myriad of molecules, but the relative amounts of these molecules to one another can vary widely. The further inclusion of therapeutic agents, with inherently different physical properties (e.g. lipophobic agents), within these lipsosomes represents another source of variability. Thus the theoretically possible, discreet liposome systems, as described above, is essentially infinite.

Applicant has discovered that within this infinite set of possible liposomes exist liposomes that allow for the intermediate release of specific class of therapeutic agents (e.g. lipophobic agents). Although the individual components for preparing these liposomes existed prior to Applicant's discovery, there were no "teachings" or "signposts" prior to the discovery that would allow one to select the Applicant's specific liposomal compositions to provide liposomes with useful intermediate release properties with a reasonable expectation of success. Accordingly, Applicant asserts that the invention as claimed is not obvious in light of the references cited.

CONCLUSION

The Examiner is invited to contact Applicant's Representative at the below-listed telephone number if there are any questions regarding this Response or if prosecution of this application may be assisted thereby. If necessary, please charge any additional fees or credit overpayment to Deposit Account No. 50-3503. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant hereby petitions for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extension fees to Deposit Account 50-3503.

Respectfully submitted,

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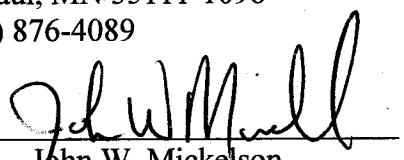
By: 
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